Atty. Docket No. TAK03 P-323

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Examiner	:	F. Prats
Applicant	:	Yoshihito Ikeda et al.
Appln. No.	:	10/018,770
Filing Date	:	December 17, 2001
Confirmation No.	:	2012
For	:	DRUG COMPOSITION CONTAINING A LECITHIN-MODIFIED SUPEROXIDE DISMUTASE

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF YOSHITOMI MORIZAWA

I, Yoshitomi Morizawa, declare the following:

1. I am a manager of Asahi Glass Co., Ltd., Tokyo, Japan.

2. During my career, I have developed expertise in various chemical technologies, including: Organic Chemistry, Organic Synthesis, Process Chemistry, Organofluorine Chemistry, Physical Organic Chemistry, Bio-organic Chemistry, Analytical Chemistry, Quality Control for Good Manufacturing Practices, and Quality Assurance for Good Manufacturing Practices.

3. I have earned a Bachelor of Science degree in Organic Chemistry/Industrial Chemistry (1975-1979) and a Master of Science degree in Organic Chemistry (1979-1981), both from Kyoto University; a scholarship in Physical Organic Chemistry from the Catholic University of Leuvain, Belgium (1982-1983); and obtained a qualification of Ph.D. in March, 1984 in Organic Chemistry from Kyoto University (1981-1984).

4. I believe that my educational and professional experiences establish that I have qualifications sufficient to state the following facts and/or opinions with confidence and conviction.

5. Phosphatidylcholine Superoxide Dismutase (also known as "Lecithin-modified Superoxide Dismutase" or "PC-SOD") is a preparation that has been developed to impart greater stability in the body and affinity with cells than unmodified SOD.

6. As described below, testing on PC-SOD has shown that PC-SOD has a different degradation mechanism from SOD (natural SOD, unmodified SOD). For example, a study of PC-SOD stability under heating conditions showed a marked change in pH. Results from mass spectrometry of the degradation products and the determination of palmitic acid have shown that this change is due to the elimination of palmitic acid from the phosphatidylcholine (PC) unit.

7. PC-SOD stability testing was performed under my supervision.

8. The PC-SOD stability testing was conducted on 15 mL samples of PC-SOD in closed, screw-capped borosilicate glass vessels (25 mL DURAN vessel, SCHOTT).

9. The tests were conducted by depositing 15 mL of PC-SOD into each test vessel, closing the vessel in ambient atmosphere, and heating the closed vessel and the PC-SOD contained therein at 25°C, 40°C, and 60°C.

10. Sample vessels maintained at 25°C and 40°C were opened after 1, 3, 7, 14, and 30 days, and the pH value of the contents were measured immediately after the vessels were opened. Sample vessels maintained at 60°C were opened after 1, 3, 7, and 14 days, and the pH values of the contents were measured immediately after the vessels were opened.

11. The results of the PC-SOD stability tests are presented graphically in Figure 1.

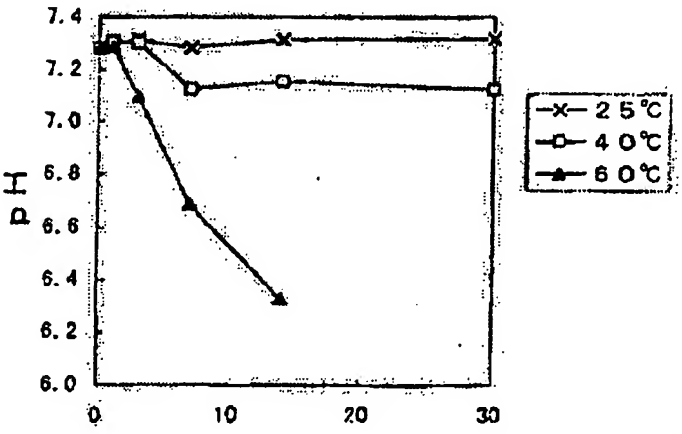


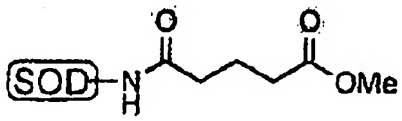
Figure 1 pH changes of PC-SOD under heating conditions

12. Figure 1 shows that the pH varied in proportion to the storage period at 40°C and 60°C.

13. The results in Figure 1 strongly suggest that PC-SOD degradation occurs by a process involving decomposition of PC-SOD into products comprising an acidic compound.

14. Mass spectrometry suggests that the degradation products include analogs A and B shown in Figure 2.

Analogue A



Analogue B

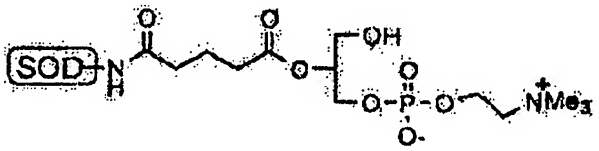
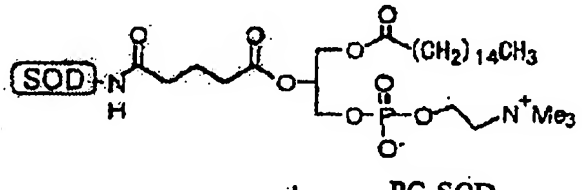
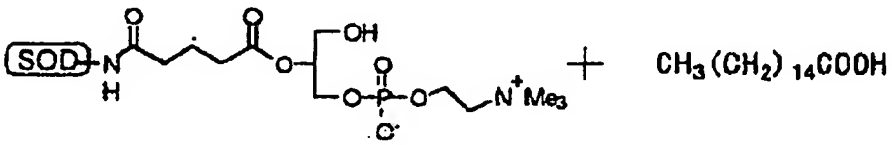


Figure 2 Analogues presumed by mass spectrometry

15. It is my opinion that a person of ordinary skill in the art would deduce from these results that the rise in acidity (lowering of pH) during the PC-SOD stability testing occurred as a result of liberation of palmitic acid from the decomposition of the PC unit, as illustrated in Figure 3.



PC-SOD



Analogue B Palmitic acid

Figure 3 Liberation of palmitic acid as a result of decomposition of the PC unit

16. Tests for determining the palmitic acid content of the degradation products were conducted under my supervision.

17. Palmitic acid content in the degradation products of PC-SOD were determined for samples stored at 40°C for 14 days and 30 days. The concentration of palmitic acid was initially below assay limit (the assay limit is 0.12 percent), but increased to 3.89 percent after 14 days and 7.90 percent after 30 days.

18. Unmodified SOD cannot release palmitic acid during degradation, since unmodified SOD does not have PC units or any other moiety from which palmitic acid can be liberated.

19. Therefore, testing has shown that, unlike SOD, the elimination of palmitic acid from the PC unit is one of the mechanisms of decomposition of PC-SOD.

20. It is reported in the literature (*e.g.*, United States Patent No. 4,966,774 at column 1, lines 27-32) that SOD degradation is "caused by polymerization."

21. Those having ordinary skill in the art could reasonably expect that agglomeration or polymerization of PC-SOD is not a predominant degradation mechanism due to steric hindrance and different surface functionalities caused by the PC unit.

22. Accordingly, it is my opinion that those having ordinary skill in the art, knowing that sucrose inhibits degradation of unmodified SOD, would not expect sucrose to inhibit degradation of PC-SOD. To the contrary, it is my opinion that those having ordinary skill in the art, taking into consideration the chemical differences and resulting degradation mechanisms, would not have predicted that sucrose could inhibit degradation of PC-SOD.

23. I declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true, and further, these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. §101, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

December 10, 2004
Date

Yoshitomi Morizawa